Diabetic kidney disease

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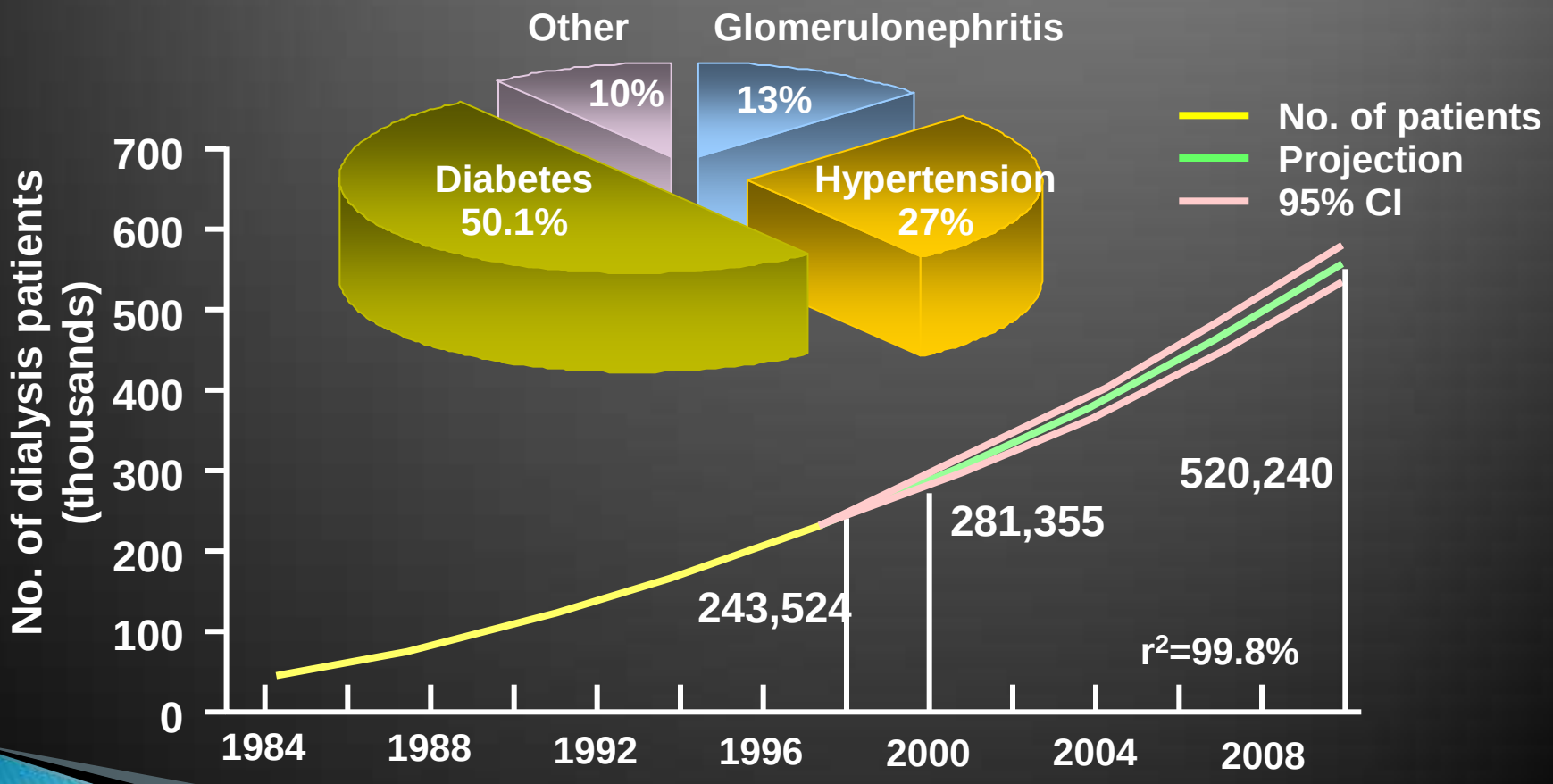
Diabetes: The Most Common Cause of ESRD

Primary Diagnosis for Patients Who Start Dialysis



United States Renal Data System. Annual data report. 2000.

Definition

The "typical" classic definition of diabetic nephropathy has previously included persistent macroalbuminuria (>300 mg/24 h or >200 μg/min) that is confirmed on at least 2 occasions 3-6 months apart , the presence of diabetic retinopathy, and the absence of nondiabetic renal diseases.

E.V. Lerma and V. Batuman (eds.), *Diabetes and Kidney Disease.* Atypical Presentations of Diabetic Nephropathy and Novel Therapies. Springer Science+Business Media New York 2014

Screening

At least once a year, assess urinary albumin (e.g., spot urinary albumin–to– creatinine ratio) and estimated glomerular filtration rate in

- Patients with type 1 diabetes with duration of 5 years
- Patients with type 2 diabetes since diagnosis
- All patients with comorbid hypertension.

Diabetes care, ADA guidelines 2016.

The prevalence of normoalbuminuria in subjects with T2DM and GFR <60 mL/min/1.73 m² was reported to be 39 %.

For hyperglycemic subjects with GFR between 60 and 89 mL/min, the prevalence of normoalbuminuria was reported to be 51 % .

The discordance between albuminuria and GFR argues against using the urinary AER as a marker for renal injury and has led to a search for a different biomarker of diabetic nephropathy.

Parving HH, et al. Prevalence and risk factors for microalbuminuria in type 2 diabetic patients: a global perspective. Diabetologia. 2004;47 Suppl 1:A64.
Bakris G, Microalbuminuria and hyperglycemia: the changing landscape ofchronic kidney disease (CKD). Diabetes. 2005;54 Suppl 1:A54.

Recent markers

Connective tissue growth factor (CTGF), transforming growth factor-β (TGF-β), and tumor necrosis factor-α (TNF-α)

The number of CTGF messenger RNA positive cells in the kidney biopsy was closely related to the renal biopsy fibrosis score

Jaffa AA et al,The Journal of Clinical Endocrinology & Metabolism. 2008;Vol. 93(No. 5):1893–1900.

Proteomic analysis

Proteomics is the large-scale study of proteins, particularly their structures and functions proteomic analysis of multiple compounds in biological fluids help screening, diagnosing disease, unraveling pathophysiology, monitoring treatments, and establishing prognosis.

Proteomics allowed detection of differences in the urinary proteome between normo, micro and macroalbuminuric diabetic patients and differentiated them from other chronic renal diseases.

Haubitz M, et al. (2009) Identification and validation of urinary biomarkers for differential diagnosis and evaluation of therapeutic intervention in ANCA associated vasculitis. Mol Cell Proteomics 8: 2296–2307

CKD273 classifier

A recently developed classifier based on 273 urinary peptides identified in the urinary proteome (CKD273) which reliably allowed specific detection of CKD.

CKD273 classifier overcame the predominant patterns related to specific diseases, and identified CKD independently of the aetiology

Good DM, et al. (2010) Naturally occurring human urinary peptides for use in diagnosis of chronic kidney disease. Mol Cell Proteomics 9: 2424–2437

CKD273 classifier

Urinary Proteomics for Early Diagnosis in Diabetic Nephropathy

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Diabetes 2012 Dec; 61(12): 3304-3313. http://dx.doi.org/10.2337/db12-0348

CKD273 classifier

the CKD273 classifier was able to predict development of DN before patients developed microalbuminuria.

The CKD273 classifier identified progressors in 65% of the case subjects earlier than the classical parameter UAER; on average, the CKD273 classifier was 1.5 years earlier than microalbuminuria.

Micro RNAs

Are small noncoding RNAs regulate the expression of genes encoding proteins implicated in the pathogenesis of DN such as TGF-b.

Measurement of plasma and/or urinary miRNAs might become useful in enhancing the prediction of diabetic nephropathy.

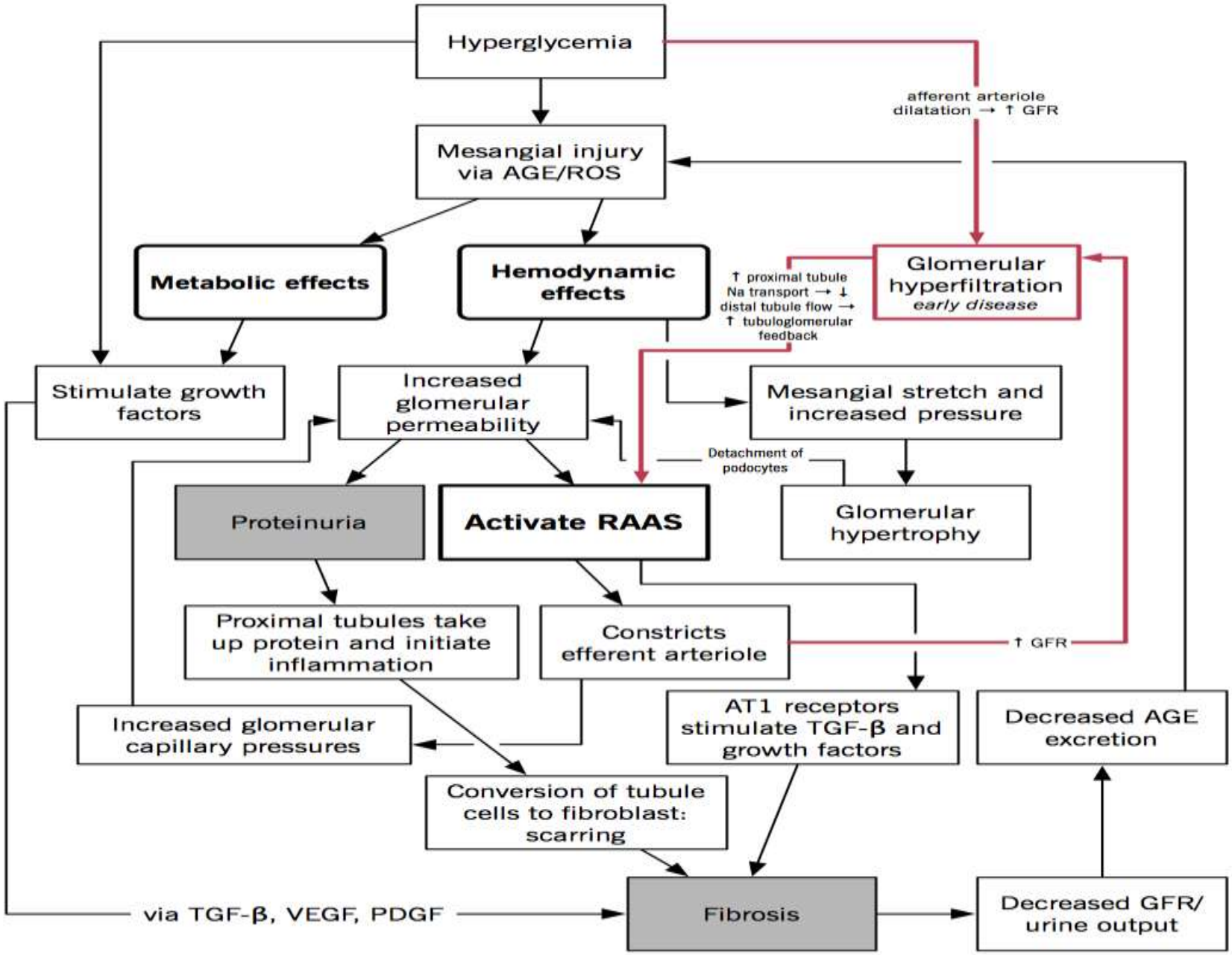
Profiling of urinary miRNAs help staging and screening, of diabetic nephropathy

Argyropoulos, C. *et al*. Urinary microRNA profiling in the nephropathy of type 1 diabetes. PLoS ONE 8, (2013).

Pathogenthesis of diabetic nephropathy

Pathophysiology of diabetic nephropathy

Eric Wong



Prevention of diabetic nephropathy

Improved glycaemic control doesn't prevent DN but clearly can attenuate the rate of progression.

Early introduction of RAS blockade in patients with normoalbuminuria doesn't prevent diabetic nephropathy.

In T2DM, particularly if there is concomitant hypertension, RAS blockade reduce the rate of progression from normoalbuminuria to microalbuminuria.

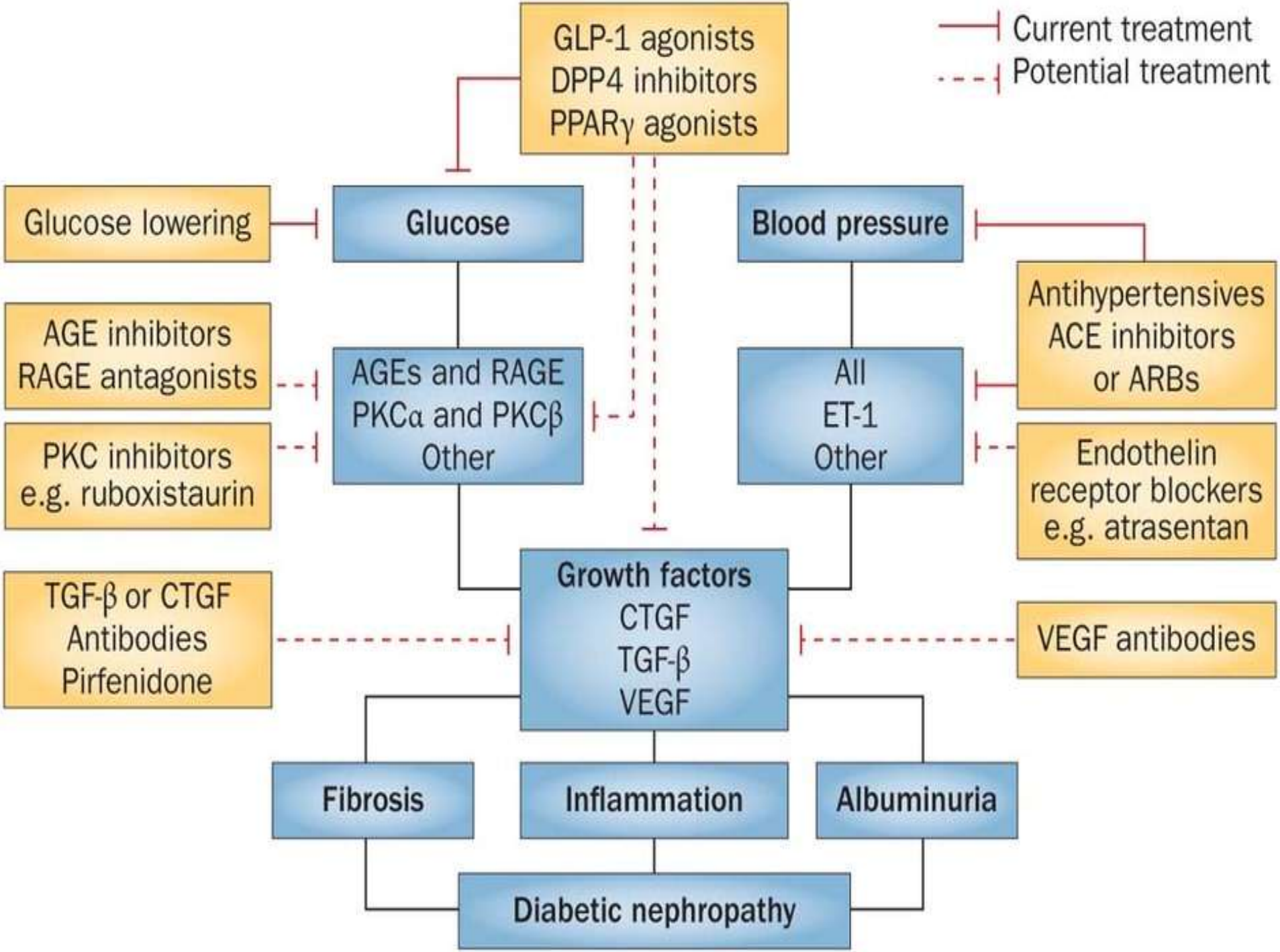
Bilous, R. *et al*. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann. Intern. Med. 151, 11–20, W3–W4 (2009).

Prevention of diabetic nephropathy

Early intervention with blood pressure lowering therapies despite modest or neutral effects on renal disease, decrease cardiovascular disease, which remains the major cause of mortality in the diabetic population.

de Galan, B. E. *et al*. Lowering blood pressure reduces renal events in type 2 diabetes. J. Am. Soc. Nephrol. 20, 883–892 (2009).

Treatment of diabetic nephropathy


Current treatment
Potential treatment
GLP-1 agonists
DPP4 inhibitors
PPARγ agonists
Glucose lowering
Glucose
Blood pressure
Antihypertensives
ACE inhibitors
or ARBs
AGE inhibitors
RAGE antagonists
AGEs and RAGE
PKCα and PKCβ
Other
AII
ET-1
Other
PKC inhibitors
e.g. ruboxistaurin
Endothelin
receptor blockers
e.g. atrasentan
TGF-β or CTGF
Antibodies
Pirfenidone
Growth factors
CTGF
TGF-β
VEGF
VEGF antibodies
Fibrosis
Inflammation
Albuminuria
Diabetic nephropathy

Mineralocorticoid receptor antagonist

Randomized studies have demonstrated that the addition of a mineralocorticoid receptor antagonist (MRA) to a renin–angiotensin system (RAS) blocker further reduces proteinuria in patients with diabetic and non-diabetic chronic kidney disease (CKD).

However, the steroidal MRAs spironolactone and eplerenone have been found to increase the risk of hyperkalemia in patients with stage 3–5 CKD by 3–8-fold.

Finerenone is a novel, non-steroidal MRA that has greater receptor selectivity than spironolactone

Bolignano D et al. Cochrane Database Syst Rev 2014;4:CD007004.

Endothelin receptor blockade
Atrasentan (xinaly abbot)

Atrasentan (xinaly) is an experimental drug that is being studied for the treatment of various types of cancer, including non-small cell lung cancer. It is also being investigated as a therapy for diabetic kidney disease.

It is an endothelin receptor antagonist selective for subtype A (ET_A). Atrasentan blocks endothelin induced cell proliferation

Endothelin Receptor Blockade

Avosentan (Roch) lowers the albumin-to-creatinine ratio by nearly 45 % and lowers BP when added to ACE inhibitors, but was associated with increasing edema and heart failure, terminating the trial

Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, Viberti G, ASCEND Study Group. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol. 2010;21(3):527–35.

SGLT 2 Inhibitors

SGLT 2 inhibitors as **dapagliflozin** are a new class of oral drugs in phase II development for the treatment of type 2 DM. Agents that block the sodium-glucose transporter-2 in the PCT allow excessively filtered glucose to be excreted in the urine— effectively lowering blood glucose levels, HbA1c, and possibly BP.

Ferannini E, et al. Dapaglifl ozin monotherapy in type 2 diabetes patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled phase III trial. Diabetes Care. 2010;3:217–24.

SGLT 2 Inhibitors

This is an insulin-independent method of lowering blood glucose. Glucose control is improved, and weight loss and BP reduction are associated with their use, with low risk of hypoglycemia.

The use of SGLT-2 inhibitors may increase the frequency of UTIs. Genital tract infections (vulvovaginitis/balanitis) were more frequent.

Abdul-Ghani MA, Norton L, DeFronzo RA. Effi cacy and safety of SGLT-2 inhibitors in the treatment of type 2 diabetes mellitus. Curr Diab Rep. 2012;12(3):230–8.

SGLT 2 Inhibitors

Modulation of tubular glucose uptake might alter generation of reactive oxygen species and influence intrarenal haemodynamics via effects on tubuloglomerular feedback, it is used early in the DN as their efficacy as glucose lowering agents is reduced in the setting of reduced GFR so it is not used in patients with advanced CKD

Vallon, V. & Thomson, S. C. Renal function in diabetic disease models: the tubular system in the pathophysiology of the diabetic kidney. Annu. Rev. Physiol. 74, 351–375 (2012).

Nrf2 (nuclear factor erythroid derived-2 like 2)

Regulates the expression of numerous genes including antioxidant enzymes, such as NADPH quinone oxidoreductase 1, glutathione S-transferase, heme oxygenase-1, glutathione peroxidase, glutamate cysteine ligase and peroxiredoxin I, which can counteract both pro-inflammatory signals as well as oxidative stress.

Zhang DD. Mechanistic studies of the Nrf2-Keap1 signaling pathway. Drug Metab Rev. 2006;38(4):769–89

Bardoxolone

The main mechanism of action of bardoxolone is the activation of Nrf2

Pareek TK, et al. Triterpenoid modulation of IL-17 and Nrf-2 expression ameliorates neuro-inflammation and promotes re-myelination in autoimmune encephalomyelitis. Sci Rep. 2011.

American Journal of Nephrology

Am J Nephrol 2013;37:208–211
DOI: 10.1159/000346950

Published online: February 28, 2013

The Extinguished BEACON of Bardoxolone: Not a Monday Morning Quarterback Story

John A. Tayek[a] Kamyar Kalantar-Zadeh[b–d]

Bardoxolone

Reductions of serum creatinine and increased GFR in diabetic patients with CKD.

The effects may relate to the blockade of oxidative damage, a hemodynamic effect, or to the ability to stimulate AMPK binding mTOR.

Unfortunately while bardoxolone increased GFR it also increased proteinuria.

Tayek JA, Kalantar-Zadeh K. The extinguished BEACON of bardoxolone: not a Monday quarterback story. Am J Nephrol. 2013;37(3):208–11.

Adverse effects	Comments
Weight loss	Not clear if fat loss is more or less than muscle loss May lead to a drop in serum creatinine leading to erroneously estimated low eGFR
Proteinuria	Can be related to hyperfiltration as a result of increased intraglomerular pressure
Increased GFR	May be similar to hyperfiltration in early diabetic nephropathy or due to erroneous estimate of GFR related to using serum creatinine
Muscle spasm	May be related to hypomagnesemia or damage to myocytes and muscle wasting
Hypomagnesemia	Apparently no obvious association with potassium disarrays Impact on QT interval in ECG was not well established
Gastrointestinal effects	Mild-to-moderate intolerance of undetermined significance but in real world scenario could become a major side effect
Liver function disorders	Increased level of alanine aminotransferase without further data
Anti-inflammatory effect	Generally is assumed to be a favorable effect, although long-term effects such as increased risk of leukemia or tuberculosis risk are not known
Increased death risk	The main cause of BEACON Study discontinuation The death etiology is yet to be determined

Pirfenidone

Another anti-inflammatory, antifibrotic agent, pirfenidone, has been found to be effective in animal models of kidney disease. Anti-TGF-β-mediated antifibrotic approaches have been shown in mouse models of kidney disease. A multicenter phase-2 trial of an anti-TGF- β-1-specific antibody in patients with diabetic kidney disease is currently ongoing.

Ziyadeh FN et al, . Long-term prevention of renal insufficiency, excess matrix gene expression, and glomerular mesangial matrix expansion by treatment with monoclonal anti-transforming growth factor-beta antibody in db/ db diabetic mice. Proc Natl Acad Sci U S A. 2000;97:8015–20.

MICRORNA Therapy

miRNA such as miR-192 is up-regulated in diabetes, possibly induced by hyperglycemia and/or TGF-β. miR-192 is the master regulator of other key renal miRNAs and downstream genes, which regulate TGF-β signaling for renal mesangial cell fibrosis. RNA-based therapeutics for blocking disease associated genes and noncoding RNAs such as chemically modified oligonucleotide (oligo) small interfering RNAs (siRNAs) and anti-miRNAs have been used before.

Ziyadeh FN, Hoffman BB, et al, Long-term prevention of renal insuffi ciency, excess matrix gene expression, and glomerular mesangial matrix expansion by treatment with monoclonal anti-transforming growth factor-beta antibody in db/ db diabetic mice. Proc Natl Acad Sci U S A. 2000;97:8015–20.

MICRORNA Therapy

Treatment with locked nucleic acid (LNA)-anti-miRNA-192 down-regulated the mRNA expression of key extra-cellular matrix-associated pro-fibrotic genes such as collagen Iα2 (COLA42), COLA41, TGF-β, CTGF and fibronectin. The cumulative effect of LNA-anti miRNA-192 was a decrease in kidney injury and an improvement in proteinuria .

Putta S, Lanting L, Sun G, Lawson G, Kato M, Natarajan R.Inhibiting MicroRNA-192 ameliorates renal fibrosis in diabetic nephropathy. J Am Soc Nephrol. 2012;23:458–69.

Modification of m-Tor Pathway

Activation of AMPK by AMPK activators as calorie restriction, exercise, metformin, or rosiglitazone offer renoprotection and cardiovascular protection.

Metformin activates AMPK (amp-activated protein kinase) and orchestrates the regulation of pathways that consume or generate ATP

Hung AM, et al. Comparative effectiveness of incident oral anti-diabetic drugs on kidney function. Kidney Int. 2012;706:681-698.

Modification of m-Tor Pathway

2 different mTOR complexes, mTORC1 and mTORC2. Activation of mTORC1 in podocytes by genetic deletion of an upstream negative regulator led to many changes of DN including albuminuria, glomerular basement membrane widening, podocyte loss, mesangial expansion and glomerular mesangial accumulation of fibronectin and collagen IV.

Godel M, et al. Role of mTOR in podocyte function and diabetic nephropathy in humans and mice. J Clin Invest. 2011 Jun;121(6):2197–209

Modification of m-Tor Pathway

Rapamycin binding to the intracellular receptor, FK-506-binding protein FKBP12, inhibits mTORC1.

Inoki K, et al. mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice. J Clin Invest. 2011 Jun;121(6):2181–96

PKC inhibitor

Hyperglycaemia activates the key intracellular signalling kinase, protein kinase C (PKC). The PKC family of enzymes includes numerous isoforms, of which the PKCα and PKCβ isoforms. A relatively specific inhibitor of the PKCβ isoform, ruboxistaurin, was demonstrated to be renoprotective in experimental models, particularly in relation to renal fibrosis.

Tuttle, K. R. *et al*. The effect of ruboxistaurin on nephropathy in type 2 diabetes. Diabetes Care 28, 2686–2690 (2005).

PKC inhibitor

Human studies with this agent have been rather disappointing.

Inhibitors of the PKCα isoform has also been tested in preclinical studies, and beneficial effects on albuminuria have been detected, predominantly via actions on VEGF.

The generation of a combined PKCα/β inhibitor, with preclinical studies suggesting that such an approach would be antifibrotic and decrease albuminuria.

Menne, J. et al. Dual inhibition of classical protein kinase C-α and protein kinase C-β isoforms protects against experimental murine diabetic nephropathy. Diabetes 62, 1167–1174 (2013).

AGE and RAGE

Specific AGE inhibitors such as aminoguanidine and pyridoxamine are agents renoprotective in the experimental studies.

RAS blockers also seem to act, at least in part, by interrupting the AGE/RAGE axis.

Thomas, M. C. *et al*. Interactions between renin angiotensin system and advanced glycation in the kidney. J. Am. Soc. Nephrol. 16, 2976–2984 (2005).

AGE and RAGE

Aminoguanidine has been studied in patients with T1DM or T2DM and renal disease but, unfortunately, despite benefits on proteinuria unacceptable adverse effects, including glomerulonephritis.

Another AGE inhibitor, pyridoxamine, continues to be investigated in phase II and III trials in patients with diabetic nephropathy

Bolton, W. K. *et al*. Randomized trial of an inhibitor of formation of advanced glycation end products in diabetic nephropathy. Am. J. Nephrol. 24, 32–40 (2004).

Uric acid lowering agents

Serum uric acid levels were reported to be increased (although still within the normal range) in patients with T1DM and microalbuminuria who progressed to overt macroalbuminuria compared with those who did not.

In addition, a cross sectional study found that serum uric acid in the high-normal range was associated with impaired renal function in patients with T1DM and normoalbuminuria or microalbuminuria.

Uric acid lowering agents such as allopurinol and febuxostat may decrease renal impairment in diabetic nephropathy.

Goicoechea M, de Vinuesa SG, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5:1388–93.

Conclusion

Hopefully, with an increasing knowledge on the pathogenesis of diabetic nephropathy some of the newer treatments currently in preclinical or clinical development will be confirmed to be renoprotective and lead to prevention, retardation or in some cases reversal of diabetic renal disease


thank you
danke
謝謝
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Баярлалаа
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